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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received November 18,2005 is acknowledged.

Claims 82, 85-87, and 90 have been amended.

Claims 82-92 are pending in the instant application.

Specification

2. The title and abstract of the instant application are objected to because they do not mention the subject matter claimed in the instant application, i.e. antibodies. Appropriate amendment of the title and abstract to better reflect the instant claimed invention is requested.

Applicant is reminded to verify, and update if necessary, the status of any pending application disclosed in the instant specification, especially those to which priority has been claimed on the first line of the specification. Specifically, it does not appear that an amendment has been entered to indicate that parent application 08/880,855 is abandoned.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

3. Claim 90 stands objected to because of the following informalities: The term interleukin is misspelled. Specifically, the claim recites "interluekin" in line 4 rather than interleukin. Appropriate correction is still required.

Claims 82 and 85-87 are also objected to due to awkward phrasing. Since it appears that the protein described in Figure 4 is SEQ ID NO:39, the examiner suggests that instead of the current "osteoprotegerin binding protein of Figure 4 (SEQ ID NO:39)" applicant amend the claims to recite "osteoprotegerin binding protein of SEQ ID NO:39" or "polypeptide of SEQ ID NO:39."

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 82-92 stand rejected under 35 U.S.C. 102(e) as being anticipated by Gorman et al. (US Patent No. 6,242,586, of record as reference B on form 892 dated March 27, 2003, see entire document) for the reasons of record set forth in the office action mailed May 18, 2005.

Applicant's arguments filed November 18, 2005 have been fully considered but they are not persuasive. Applicant's first argument is that the claimed invention cannot be anticipated because Gorman et al. do not teach the polypeptide sequence of human RANKL/TRANCE/499E9/OPGL/osteoprotegerin binding protein, hereafter designated OPGbp, which is the polypeptide encoded by SEQ ID NO:39 of the instant application. This point was discussed in the rejection of record, wherein it was indicated that due to the high degree of identity (84.1%, see enclosed search notes) between mouse and human OPGbp, the anti-mouse OPGbp antibodies taught by Gorman et al. would bind the polypeptide of SEQ ID NO:39. Applicant furthers this argument by indicating that there is no evidence to indicate that cross-reacting antibodies would bind both mouse and human OPGbp.

In response to applicant's arguments and request for evidence, applicant is invited to consider the following evidence. It would have been well known to a skilled artisan at the time of the invention that antibodies to a mouse protein can cross-react with the human homolog of that protein. Cross-reactivity is a well known immunological phenomenon wherein an antibody binds to the same epitope present on two different antigens or binds to another epitope that is chemically very similar in structure, as evidenced by the textbook Immunology (Kuby, Janis; 1992, W.H. Freeman and Company, page 125). A skilled artisan would also have known that the size of an epitope recognized by an antibody is often between 6 to 10 amino acids in length as is evidenced by the teachings of Harlow et al. (Antibodies A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, page 76, particularly the middle of the page). An

examination of the sequence alignment between SEQ ID NO:39 (human OPGbp) and mouse OPGbp indicates 84.1% identity, with numerous stretches of identity greater than 6 contiguous amino acids (see provided sequence search notes). The specification indicates that SEQ ID NO:32 is the BB' loop of mouse OPGbp while SEQ ID NO:34 is the EF loop of mouse OPGbp. When these two sequences are lined up against human OPGbp, stretches of greater than 6 contiguous amino acids can be found that are identical between the mouse and human sequences, with 88.9% identity for the BB' lop and 88.2% for the EF loop (see provided sequence search notes). As such, it is clear that mouse and human OPGbp share numerous identical epitopes that can be recognized by cross-reactive antibodies. The property of cross-reactivity is quite common and is often used advantageously to clone homologous proteins from other organisms (Liu et al., Mol Reprod Dev 1990, 25:302-308, see entire document). Further, there are presently two different commercially available monoclonal antibodies made by immunizing mice with mouse OPGbp that bind both mouse and human OPGbp (see product use sheets for clone 12A380 sold by Imgenex and clone 12A668 sold by Stressgen). Based upon all of the above, the antibodies disclosed by Gorman et al. would also bind human OPGbp even though Gorman et al. did not disclose the sequence of human OPGbp.

Applicant's final argument concerns the production of human antibodies. Applicant does not provide evidence that the teachings of Gorman et al. would not be sufficient for a skilled artisan to make and use human monoclonal antibodies, and instead argues that at best the human monoclonal antibodies of Gorman et al. would

only bind mouse OPGbp and not human OPGbp. This argument is not persuasive for the reasons discussed above.

As such, the rejection of record has been maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 82, 83, and 85-92 under 35 U.S.C. 103(a) as being unpatentable over Popoff et al. (US Patent No. 5,641,747, see entire document) as evidenced by Yang et al (PNAS (1985) 82:7994-7998, see entire document), in view of Lonberg et al. (WO 93/12227, see entire document, of record as reference BC on the IDS received March 25, 1999) has been withdrawn in view of applicant's amendments to the claims and persuasive arguments.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 82-92 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-9, 21, and 22 of copending Application No. 10/180,648. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/180,648 anticipate the instant invention for the reasons of record set forth in the office action mailed May 18, 2005.

Applicant has acknowledged this rejection in the reply received November 18, 2005, and has asked that further action be deferred until such time as there is an indication of allowable subject matter in the instant application. As such, the rejection is maintained.

10. Claims 82-92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50, 52, and 53-73 of copending Application No. 10/408,901. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the claims of copending application 10/408,901 anticipate the genus of antibodies claimed in the instant invention because the copending claims recite antibodies of a specified heavy and light chain sequence. Note that these antibodies are claimed as being fully human (see particularly claim 49). Note also that the specification of the copending application discloses on page 70 that the antibodies of the copending application bind human OPGbp.

This is a provisional obviousness-type double patenting rejection.

11. Claims 82-92 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-53 of copending Application No. 09791,153 in view of Lonberg et al. (of record on the 892 mailed May 18, 2005.

The claims of copending application 09/791,153 recite antibodies comprising specific Fab sequences that bind human OPGbp, and indicate that these antibodies comprise human Fc domains (see particularly claims 12 and 13). These claims differ from the instant invention in that they do not teach that the antibodies of a defined sequence (i.e. monoclonal) are human.

Lonberg et al. teach that human antibodies offer an advantage over all other antibody type for *in vivo* diagnostic and therapeutic use in that the use of human antibodies reduces anti-therapeutic antibody responses, including HAMA responses (see particularly page 1, lines 27-38). Such responses are generated due to the

inherent immunogenicity of non-human immunoglobulins. When non-human antibodies are administered to a human patient, the patient's immune system produces antibodies that neutralize the efficacy of the therapeutic antibodies, and the resulting antibody complexes can also cause acute toxicity (see particularly page 1, lines 27-38). Human antibodies would not be highly immunogenic in human patients, and as such unwanted anti-antibody responses could be reduced (see particularly page 1, lines 27-38).

Therefore, a person of ordinary skill in the art would have been motivated to make the antibodies recited in the claims of copending application 09/791,153 as human antibodies to gain the advantage of having an antibody of very low immunogenicity that does not elicit unwanted anti-therapeutic antibody responses in the patient such that it can be used in methods of administration to human patients.

This is a provisional obviousness-type double patenting rejection.

12. In reviewing the instant application in response to applicant's reply and amendment received November 18, 2005, the examiner identified additional copending applications that list William Boyle among the inventors and claim subject matter substantially identical to that claimed in the instant application. As such, applicant was aware of these related applications, and the subject matter claimed therein, prior to this office action. Further, the examiner could not find any indication that applicant has disclosed the potential for duplicative subject matter in these related cases in the prosecution history of the instant application through their inclusion as part of an Information Disclosure Statement. As such, this action has been made final.

Note that the instant application is senior to all of the applications with potentially conflicting subject matter and as such failure to distinguish the instant claims from the claims of the other applications and/or failure to file appropriate terminal disclaimers would not impede allowance of the instant claims if provisional obvious-type double patenting rejections are the only remaining rejections of record.

13. No claims are allowable.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 26, 2006

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